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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/918,288	08/25/97	BOIME	1 295002005025

EXAMINER

HM11/1221

MORRISON AND FOERSTER
2000 PENNSYLVANIA AVENUE N W
WASHINGTON DC 20006

ART UNIT	PAPER NUMBER
1646	8

DATE MAILED: 12/21/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 10/19/98

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days~~, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-40 is/are pending in the application.
Of the above, claim(s) 2,10,12,20,22,30,32,40 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1,3-9,11,13-19,21,23-29,31,33-39 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☒ Claim(s) 1-40 are ~~are~~ subject ~~to restriction or~~ election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3,4
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Part III: Detailed Office Action

Species Election Requirement:

Applicants have elected to prosecute species 10 from Table 1, n-hFSHβ(1-104)-Linker-humanα(1-92)-c. Applicants have incorrectly identified the claims corresponding to the elected species. The correct identification of such is: 1, 3-9, 11, 13-19, 21, 23-29, 31, 33-38 and 39. It is noted that claim 7 encompasses the elected species, which has a truncated FSHβ subunit.

Claims 2, 10, 12, 20, 22, 30, 32 and 40 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to non-elected species, election having been made without traverse in Number 7, filed 10/19/98. Claims 1, 3-9, 11, 13-19, 21, 23-29, 31 and 33-39 are under consideration.

Sequence Compliance:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825 within the statutory period set forth for response to this Office Action. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Formal Matters:

The disclosure is objected to because of the following informalities. Appropriate correction is required for *each* listed item:

- The status of the related applications to which reference is made at page 1§1 of the specification should be updated.

- The specification is objected to for failing to provide support for a linker which is a gly-ser repeat or a linker having from 1-16 or 1-100 amino acids.

-Table 1, which appears at page 53 of the specification, should appear at or near the first reference to such, at page 34. Additionally, Table 2 should appear at or near the first reference to such in the specification. With further regard to Table 2, the Examiner is unable to find *any* reference to such in the specification as filed. If such is not the case, applicants are requested to point out such reference to the Examiner. If such *is* the case, correction is required.

- The description of the properties of analog 3, at page 38, may be in error. The specification states that the protein "is tested for its ability to inhibit the binding of radioiodinated hCG to monoclonal antibodies or to antisera prepared against hCG. It is not clear why such a test would be conducted, nor what the results of such would indicate, as analog 3 is an LH, and not a hCG analog.

The language "partial CTP unit or variant thereof", such as appears in claim 6, is not limiting as concerns any particular amino acid sequence. The specification as filed has no clear definition of a "partial CTP unit". As there is no functional limitation on such, nor any limitation on minimal length, the Examiner concludes that this definition includes any "partial CTP unit" which is as short as a dipeptide, such being the shortest possible "sequence" of amino acids. The claim includes not only all such "partial CTP" units, but "variant thereof". A variant being a sequence having one or more substitutions, it follows that a "variant" of a "partial CTP unit", when read in light of the specification, may have no sequence nor property in common with a CTP unit. As such, those

sequences falling within the metes and bounds of such language are not limited, and art will be applied accordingly.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is indefinite because it is self-referential.

Rejections Over Prior Art:

Determination of priority: Claims 5, 15, 25 and 35, which recite that the linker unit is a gly-ser repeat, and claims 14, 24 and 34, which limit the linker to 1-16 amino acids, merit priority to the filing date of application 08/853524, 5/9/97. The specific formulae recited in Table 1, as recited in claims 9, 19, 29 and 39, merit priority to the filing date of application 08/853524, 5/9/97. The remaining claims under consideration, claims 1, 3, 4, 6-8, 11, 13, 16-18, 21, 23, 26-28, 31 33, and 36-39, merit priority to parent application serial number 08/289396, filed 8/12/94.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims

under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a). Earliest priority 2/18/94

Claims 1, 4, 8, 11, 14, 18, 21, 24, 28, 31, 34 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomason, U.S. Patent number 5,705,484 (4/1/93) in view of Reddy et al., WO 85/01959 (5/5/85), (Reddy-1) cited by applicants, and U.S. Patent number 4,923,805, also to Reddy et al. (1/30/85) (Reddy-2).

Thomason teaches a polypeptide in which "at least two monomeric polypeptide subunits of a naturally occurring multimeric protein are linked together as a single polypeptide ("fusion multimer")" (column 2, lines 55-59). The advantages of such are that they are more easily and rapidly refolded than unfused multimers, and the elimination of undesired by-products (col. 2 lines 60-67). At the top of column 3, Thomason states that the subunits may be directly linked or may be separated by a spacer moiety. Thomason envisions both biologically active fusion multimers, as well as fusion multimers that function as inhibitors of the native protein (col. 4, lines 21-30, col. 5 lines 62-63). Thomason's preferred species was PDGF, however the disclosure clearly contemplates any multimeric protein, see column 3 beginning at line 45. The exemplified host cell was *E. coli*, see Examples 5 and 6, column 16. Thomason neither teaches nor suggests a nucleic acid encoding a fusion multimer protein comprising a glycoprotein hormone.

Reddy-1 teaches the recombinant production of glycoprotein hormones, including hCG, including the use of *E. coli* as the host cell for such recombinant production.

Reddy-2 teaches DNA encoding the human βFSH subunit, and recombinant production thereof.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute the glycoprotein hormones disclosed by Reddy et al. in the method of Thomason, that is, to produce nucleic acids encoding fusion multimer glycoprotein hormones, and

then make transformed cells comprising such and use such for the recombinant production of such. The person of ordinary skill in the art would have been motivated to do so by the disclosed advantages of such as pointed out by Thomason and reiterated above, namely favorable renaturation kinetics and stability. One of ordinary skill in the art would immediately have recognized, upon reading Thomason's disclosure that the method would be reasonably expected to be successful for any dimeric protein, with or without a linker sequence, as disclosed by Thomason. With respect to the order of the subunit, Thomason merely discloses that they be arranged "head to tail", see col. 3 line 2. The Examiner finds that it would have been routine experimentation to determine functional orientation of the subunits, e.g. α-β or β-α, and that either orientation is considered to be obvious over Thomason's disclosure. With respect to claim 14, which recites a specific linker length of 1-16 amino acids, such is considered obvious over Thomason, as the optimization of linker length is clearly considered by Thomason to constitute routine experimentation. As such, it would be obvious to use a linker within that range.

Claims 7, 9, 17, 19, 27, 29, 37 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomason, U.S. Patent number 5,705,484 in view of Reddy et al., WO 85/01959, (Reddy-1) cited by applicants, and U.S. Patent number 4,923,805, also to Reddy et al. (Reddy-2) as applied to claims 1, 4, 8, 11, 14, 18, 21, 24, 28, 31, 34 and 38 above, and further in view of Zurawski et al., EMBO Journal 7(4):1061-1069, 1988.

The elected species has a truncated β subunit, having 104, as opposed to the wild-type 111 amino acids. Neither Thomason nor either of the Reddy references teaches of suggests such a truncation.

Zurawski et al. teach fine structural deletion analysis, which was used to identify critical regions within mouse Interleukin 2 (IL-2). Numerous deletion mutants of IL-2 were constructed and expressed using recombinant DNA methodology, and assayed for biological activity (see Fig. 2). At page 1067, second column, Zurawski et al. teach that their method has general utility for the fine structure mapping of proteins, and that "the method unambiguously identifies regions that are

unimportant to the activity of the protein."

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to apply the deletion analysis taught by Zurawski et al. to the FSHβ taught by Reddy-2 to identify "unimportant regions", and then to substitute such deletion mutants lacking such "unimportant regions" in to the nucleic acids found obvious over Thomason et al. in view of Reddy-1 and Reddy-2, above. The person of ordinary skill in the art would have been motivated to make such a substitution in view of Zurawski's teaching of the general utility of the method, especially for proteins that are recognized by receptors (see page 1067, second column), as is the hormone FSH. Accordingly, it would have been obvious to substitute any deletion mutant having the desired property, which deletion mutant itself is obvious over Reddy-2 in view of Zurawski, into the method of Thomason et al. Therefore, in the absence of evidence to the contrary, the elected species, having a 7 amino acid deletion from the carboxyl terminus of the β subunit of FSH, appears to be *prima facie* obvious over Thomason, Reddy-1, and Reddy-2 in view of Zurawski et al.

Claims 3, 6, 13, 36, 23, 26, 33 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomason in view of Reddy-1 and Reddy-2 as applied to claims 1, 4, 8, 11, 14, 18, 21, 24, 28, 31, 34 and 38 above, and further in view of Fares et al., cited by applicants, or Boime, U.S. Patent number 5,585,345.

These claims introduce the limitation that the linker unit is CTP, the carboxy-terminal peptide of hCGβ. Fares et al. disclose that fusion of CTP to FSHβ increases the *in vivo* serum half-life and biologic activity of the chimeric protein (page 4307, second column, for example). Boime discloses and claims CTP extended forms of FSH, LH and TSH beta subunits. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute the FSHβ-CTP fusion of Fares et al. or the FSHβ-CTP, TSHβ-CTP or LHβ-CTP of Boime in the construct found obvious above over Thomason in view of Reddy-1 and -2, for the same reasons as above, namely, favorable renaturation kinetics and stability. It is noted that such a construct, when in the β-α

orientation, would meet the structural limitation of having a CTP linker sequence.

Claims 5, 15, 25 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomason in view of Reddy-1 and -2 as applied to claims 1, 4, 8, 11, 14, 18, 21, 24, 28, 31, 34 and 38 above, and further in view of Chaudhary et al., Nature 339:394, June 1989 and Cousens et al., U.S. Patent number 4,751,180.

These claims introduce the limitation that the linker sequence is comprised of glycine and serine residues, specifically a gly-ser repeat.

The above references make no suggestion as to the nature of the linker sequence. Chaudhary et al. disclose the use of a 45 base pair linker for connecting two antibody variable domains in a fusion protein. The linker encoded a 15 residue long stretch of gly and ser residues, see Fig. 1a. Cousens et a. disclose that non-polar amino acids such as Gly and Ser are useful in a linker, therein a 'flexible hinge' region, see column 4. While it is noted that Cousens et al. were using the hinge to keep binding proteins *away* from each other, it is the teaching that non-polar amino acids make a flexible linker that is relevant.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use a flexible linker comprising gly and ser residues, as taught by Cousens et al. and Chaudhary et al. as the linker in the constructs of Thomason in view of Reddy et al. One of ordinary skill in the art would have been motivated to do so in view of Cousens' disclosure that such makes a flexible sequence, and would immediately have recognized that such flexibility would be desirable in the construct of Thomason in view of Reddy et al., in which such flexibility would be reasonably expected to aid in allowing the individual portions of the fusion protein to align for proper dimerization, the linker function suggested by Thomason. The cited references render obvious *any* arrangement of gly and ser residues, thus the particularly recited sequence of claim 5 is *prima facie* obvious over the cited prior art.

The prior art made of record and not relied upon is considered pertinent to applicant's

disclosure.

Xia et al., J. Mol. Endocrinol. 10:337, disclose muteins of hCGβ.

Narayan et al., Mol. Endocrinol. 9:1720, 1995 discloses "yoked" hCG, in which a single chain hCG was made. Two forms were made, hCG1, having the complete β subunit, and hCG2, having only the N-terminal 123 amino acids of the β subunit.

Chappel et al., U.S. Patent number 5,352,779 disclose recombinant production of glycoprotein hormones having altered glycosylation sites.

Double Patenting:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of copending Application No. 08/853514 in view of Thomason, Reddy-1 and Reddy-2 .

The instant claims are drawn to nucleic acids which encode the proteins of the copending application. It is noted that no restriction requirement was required between these two inventions. The person of ordinary skill in the art, reading the claims of the copending application, would immediately realize that the most efficient and reliable way to obtain the proteins claimed therein is through the use of recombinant DNA technology. The Reddy and Thomason references provide the necessary elements to achieve such, namely the sequences encoding the hormone subunits which

make up the proteins claimed in the copending application, as well as the general discussion of Thomason of the recombinant production of such fusion proteins. Sequence encoding any particularly recited linker sequences such as a gly-ser repeat, could be arrived at by the person of ordinary skill in the art using knowledge old and routine in the art, namely a table of correspondence of codons to amino acids. Therefore, the instantly claimed nucleic acids, host cells, and expression methods are *prima facie* obvious over the proteins claimed in the copending application.

This is a provisional obviousness-type double patenting rejection.

Advisory Information:

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 8:00 A.M. to 4:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Lila Feisee, can be reached at (703)308-2731.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 305-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. **Please** advise the Examiner at the telephone number above when an informal fax is being transmitted.

Lorraine Spector

Lorraine Spector, Ph.D.
Primary Examiner

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